Our Reference: BB-IND [---

[----------

Dear [----------

We have reviewed the August 22, 2000, submission to your **Investigational New Drug Application (IND)** for [----------
[----------

March 6, 2000 Gene Therapy Letter. Your response to item 6 of our letter is inadequate and we have the following comments and requests for additional information:

CLINICAL MONITORING

1. Please provide a list of each study, according to the study title, conducted under this IND. For each study, please state whether the study is closed, closed to accrual but contains patients under active treatment, or actively recruiting.

2. If all studies are closed (i.e., accrual completed and no patients under active treatment), please confirm that a complete description of the clinical monitoring program, as described in the March 6, 2000 letter, will be submitted when a new protocol is submitted or re-treatment of previously enrolled subjects is contemplated.

3. Please provide a description of your clinical trial monitoring program, which includes a description of the personnel responsible for monitoring and a summary of the procedures for clinical study conduct, monitoring, and auditing. Your program should permit you to fulfill all the responsibilities as outlined in 21 CFR 312 subpart D.
   The program should provide, at minimum, information regarding the following aspects of your clinical trial monitoring program:

   a. Please describe how you monitor for:

      1) Adherence to the protocol-specified study eligibility.

      2) Adherence to the protocol-specified treatment plan.

      3) Adherence to the protocol-specified data collection for safety and efficacy.

4) Adherence for reporting of adverse events to: IRB, sponsor or to FDA (if you are both the sponsor and principal investigator), and the NIH/OBA, including adherence to required timeframes.

5) Adherence to informed consent requirements (including verification that written and other informed consent materials have been approved by IRB; are signed prior to entry into study; and appropriate witnesses documented).

b. Please describe how you ensure that any modification to the study plan has been submitted to the FDA and the IRB prior to implementation, as required, and that the IRB has approved the changes prior to implementation.

c. Please confirm that final, audited study reports are submitted to FDA and the IRB within a reasonable timeframe. Describe the procedures for verification of the accuracy of the final study data by comparison against the primary source documents. Also, confirm that a complete set of source documents is maintained.

d. Please describe the procedures for monitoring and auditing of data that:

1) Are established for the correction of errors in the study reports. This procedure should preserve the original record and identify the date of correction, individual making the correction, and reason.

2) Identify the individuals responsible for performing monitoring and completion of study report forms and also identifies individual(s) with authority for final verification (sign-off) of study records.

3) Are established for receipt and tracking of investigational drug product; please identify the individuals responsible for tracking investigational drug product.

4) Are established for closing study sites or removing investigators for failure to adhere to protocol.

e. Please provide an organizational chart that:

1) Identifies the individual(s) and/or organization with responsibility for monitoring the clinical study or clinical program.

2) Summarizes the duties of each individual who has monitoring/oversight responsibilities.

3) Provide the reporting relationship between the study monitor/monitoring organization and the IND sponsor.

4) Indicates that the sponsor has adequate oversight of the conduct of the Clinical study.

f. If any of the duties have been transferred to a contract research organization or other party, please identify the subcontractor, enumerate those responsibilities which have been transferred, and provide documentation from the subcontractor which acknowledges their role in the clinical program.

g. Provide a description of the qualifications (training, experience, and/or certification) for each member of the monitoring program. For those individuals with certification or accreditation, identify the certification/accreditation program name and specify the date certified
or accredited.

h. Provide a summary description of the extent and frequency of the monitoring/auditing program. Identify the types of primary source documents (e.g., patient charts, lab reports) that are reviewed to verify the accuracy of the case report forms or other data listings, specify the proportion of primary source documents reviewed for each study patient, and specify whether source documents are reviewed for each study patient. If there is more than one clinical study site, indicate whether the frequency and extent of on-site study monitoring and auditing are identical at each study site. If differences exist, provide the information separately for each study site, and provide your justification for different standard procedures.

i. Please list any recent changes to the clinical monitoring program and reason for those changes.

The above information is necessary to assess the risks to subjects in your studies and should be submitted by **December 10, 2000** for review by FDA. This letter serves as notice to you that failure to submit the information within this time frame will result in a clinical hold on this IND and other INDs that may cross-reference your IND. The response to items 1 through 5 and 7 is still under review. If we have additional comments or questions, we will contact you. Please prominently identify on your cover letter "RESPONSE TO GENE THERAPY LETTER" and submit this information in triplicate to the IND. In your reply to this letter, we request that you restate each above question or comment and follow it with your explanation or clarification. Use of this format helps organize the relevant information and provides a self-contained document that facilitates review and future reference.

If you have any questions, please contact the Regulatory Project Manager, Andrea Wright, at

(301) 827-5101.

Sincerely yours,

Glen D. Jones, Ph.D.
Director
Division of Application Review and Policy
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

___ _____ _____
_____
_____--

---- | ------ | ------- | ---- | ------ | ------- | ---- | ------ | ------- | ---- | | |
-------- | | | | | | | | | | | |
| | | | | | | | | | | |
| | | | | | | | | | | |